

Chemotherapy: Is it Warranted in Curable Head and Neck Cancer?

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ABSTRACT

Since the last century, many physicians have been trying to utilize chemotherapy to replace conventional surgical treatment for cases of cancer of the oropharynx, larynx, and hypopharynx, which would otherwise be candidates for total laryngectomy. Some authors claim that the preservation rate of the larynx increases after treatment by chemotherapy, which even may take the place of routine surgical methods. However, when calculated in a more rigorous way following accepted statistical methods, what they claim is questionable. As a result, the routine application of chemotherapy in its present form is not advisable for curable squamous cell carcinoma of the head and neck region. Further research is required to justify its benefit.

In recent decades there have been many articles advocating organ preservation strategy by using induction chemo- and radio-therapy for head and neck cancer, especially for cases of cancer of the oropharynx, larynx and hypopharynx, which would otherwise be candidates for total laryngectomy. The purpose behind all of these studies was to increase the survival rate and to preserve the larynx. After nearly 20 years of world wide clinical research, Wolf et al., in 1999, reported in an analysis of over 10,000 cases, that after utilizing chemotherapy with radiotherapy and conventional surgery “the overall survival rates were largely unchanged.”^[1] The rate of laryngeal preservation was 2/3, which he attributed to the success of combined chemo- and radiotherapy. “Head and neck oncology,” Wolf stated, “remains at a critical crossroad in defining a role for chemotherapy in the routine management of patients with advanced, potentially curable cancers.”^[1] The picture is clear, there is no beneficial effect on survival, but the preservation rate for the larynx is high. The authors reported that if there was no chemotherapy and/or radiotherapy regimen, all larynges in this series would have been removed.

Table 1 is composed of data from 8 papers reporting the results of chemo- and radiotherapy, holding total laryngectomy in reserve for failures.^[2-9] In total, there were 549 cases of Stage III and Stage IV laryngeal and hypopharyngeal cancer. One can observe from Table 1 that among all cases 131 (22%) were in T1 and T2 categories. The Journal readers would not understand why a laryngologist in

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Table 1. End results of clinical trial of chemotherapy/radiation and then surgery for failures

Authors	Sites	T Classification				Rate of Laryngeal Preservation	Year of Observation	Survival (%)
		T1	T2	T3	T4			
Demard et al. ^[2]	Larynx	1	24	24	1	32	3	62
	Hypopharynx	0	9	20	2		3	29
Wolf et al. ^[3]	Larynx	15		109	42	64	2	68
Kraus et al. ^[4]	Hypopharynx	0	8	9	8	32	2	44
Shirinian et al. ^[5]	Larynx	0	3	20	2	44	1	71
	Hypopharynx	0	6	19	4	28	1	46
	Oropharynx	0	0	4	5	25	2	38
Clayman et al. ^[6]	Larynx	0	4	21	1	67	3	56
		0	12	13	4		3	
Lefebvre et al. ^[7]	Pyriiform sinus	0	22	74	4	58(CR), 38(<CR)	5	69
Samant et al. ^[8]	Pyriiform sinus	0	4	11	10	88	5	50
Urba et al. ^[9]	Oropharynx	5	18	24	32	59	3	46
	Hypopharynx							35

1980-1990s would perform total laryngectomy on such early disease. The cancers were classified as stage III (T1, T2, N1) and stage IV because of the presence of enlarged neck nodes. For N1-2 cases, neck dissections should be mandatory, but there is no indication for total removal of the larynx for T1 and T2 categories. Even many T3 or T4 (UICC-TNM 1992 Edition) laryngeal and hypopharyngeal cancers would be treated by partial laryngectomy to preserve the function of the larynx today.^[10,11]

After in-depth study of the above papers the laryngeal preservation rate of "two thirds" (64% in Wolf's series,^[3] which included 15 cases of T1 and T2 patients) after chemotherapy and radiotherapy, seemed to be debatable. The conclusions of these studies should be:

- No improvement in survival rate as compared with routine treatment by surgery and/or radiotherapy, as Wolf and others reported.^[1,9]
- The claimed laryngeal preservation rate is questionable because a significant number of the cases (at least 131 cases from Table 1) had none of the usual indications for total laryngectomy.
- The induction chemotherapy regimen failed to offer benefits to the head and neck squamous cell carcinoma patients.

- The morbidity associated with chemotherapy and the question of cost-benefit are important factors that must be carefully considered.

These facts are in sharp contrast to the conclusions drawn in the last paragraph of Wolf's paper: "The key question of whether organ preservation with chemotherapy and radiation was an accepted alternative to laryngectomy for patients with stage III or IV laryngeal cancer was answered strongly with consensus in the affirmation."^[1]

On the other hand authors from France have published articles reporting high survival rates after the chemotherapy-alone regimen.^[12-14] Laccourreye et al. said in 1996 that "Exclusive chemotherapy for T1-T3N0M0 glottic squamous cell carcinoma did not decrease survival when compared with the conventional treatment modality of partial laryngectomy."^[12] This advance in clinical oncology might surprise many otolaryngologists, if the statistical results of this research were interpreted correctly. Or, as a result of this study will the authors use chemotherapy to replace conventional surgical treatment of today for the management of laryngeal or hypopharyngeal lesions?

The following are the extracts from 3 papers by Laccourreye et al.

In 1996, the end result of 178 glottic T1-3N0M0 patients who underwent 4-11 courses of chemotherapy (cisplatin, fluorouracil, or bleomycin) was reported.^[12] Laccourreye chose 21 cases from these 178 patients to provide the basis for his conclusion. The 21 patients were treated by chemotherapy only, and were all CR (complete responders). The remaining 157 cases were given other treatments following chemotherapy, but the modality of management, and the outcomes were not clearly stated in the article. The 5-year survival rate of these 21 patients (71.5% of the 21 cases were in T2 and T3 categories) was 95.2% (20/21). This high survival rate is clearly the result of case selection. If one makes a rigorous calculation, the 5-year survival rate of exclusive chemotherapy for complete response would be 20/178 instead of the reported 20/21. About one third of the 21 cases had local recurrences and were salvaged by additional treatment.

In 2001, another report appeared in Cancer written by Laccourreye et al.^[13] Six hundred and seven cases of laryngeal or laryngopharyngeal cancer were treated with 5-6 courses of chemotherapy (cisplatin and fluorouracil). From that group 67 cases were chosen for analysis from a total of 166 cases of CR. There were 31 cases of local recurrence salvaged by surgery and radiation. The 5-year actuarial survival estimate of the 67 cases, reported by the authors, was 71.1% (48/67). Calculated in a more rigorous way following accepted statistical methods, the 5-year success rate (excluding the 31 salvaged cases) of exclusive chemotherapy for complete response would be (48-31)/607 instead of the reported 48/67.

In 2002, 231 cases of glottic T1-T3N0M0 were reported after 5-6 courses of chemotherapy (cisplatin

and fluorouracil). From that group, 35 patients out of 77 CR patients were chosen for analysis.^[14] The 3- and 5-year actuarial survival estimates were 91.4% (35 cases) and 88.6% (29 cases), respectively. There were 12 recurrences salvaged by other modalities of treatment. If calculated properly, the 3-year success rate of exclusive chemotherapy treatment for a complete response was (32-12)/231 instead of 32/35.

The above results are summarized in Table 2.

If all the data from 3 papers were put together, only less than 10% cure rates in CR cases were obtained by chemotherapy alone. This figure does not represent a clinically useful treatment regimen and is not worth the initial morbidity, toxicity, occasional mortality, and costs involved. With conventional surgery or radiotherapy for the whole group of patients one would expect a cure rate of 60%-70% for T1-T3 cases.^[15-17]

Pignon et al., after doing meta-analysis of related chemotherapy trials, came to the conclusion that "neither adjuvant nor neoadjuvant chemotherapy provided significant benefit; therefore these modalities should not be used outside clinical trials."^[18] This is a responsible and conscientious position. One should refrain from any radical design and action of clinical research and thus save a majority of patients from unwanted and unnecessary pain and suffering.

DISCUSSION

In clinical therapeutic oncology the patient pays a price for a life-saving method of treatment. The modality used may save the cancer patient's life, but it will incur some significant undesirable consequences. The patient must live with the accompanying serious

Table 2. Summary of cases reported by Laccourreye et al.

Site of lesion	TN category	Year of case collection	Total Cases	CR after chemotherapy	Selected cases from CR for analysis (exclusive chemotherapy)	Local recurrence among selected cases of CR	5-year survival (CR only)
Glottic	T1-T3N0	1985-1992 ^[12]	178	58(30.7%)	21(11.8%)	Local control 70.7%	20/21(95.2%)
Pharyngolarynx	T1-T4N0	1981-1997 ^[13]	607	166(27.3%)	67(11.0%)	31/67(46.3%)	48/67(71.1%)
Glottic	T1-T3N0	1985-1996 ^[14]	231	77(33.3%)	29(12.5%)(5 year)	12/35(34.3%)(3 year)	26/29(88.6%)

discomfort and complications. For ordinary diseases, like peptic ulcer, the patient will be cured without any residual disability. A cancer patient may be cured by surgery, radiation, or chemotherapy, but he is never quite the same individual he was before the treatment. A radical neck dissection may cure 50% of the head and neck cancer patients, but the patients will experience some discomfort and inability to use the upper limb properly for the rest of his life. A patient with nasopharyngeal carcinoma may be cured by irradiation, but he has to endure life-long dryness of his mouth and stiffness of his neck. The conscientious physician will never carry out clinical research without careful consideration of the potential side effects and long-term consequences of the designed protocol. In Laccourreye's reports, all the patients endured the morbidity of chemotherapy yet only about 10% of the treated cases were used for calculation of the survival rate. High selection of cases for analysis is not appropriate in scientific research.

CONCLUSION

The routine application of chemotherapy in its present form is not advisable for curable squamous cell carcinoma of the head and neck region. Further research is required to justify its benefit.

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